

Compounds

This invention relates to novel compounds, compositions containing them and their use as antibacterials.

5 DE2315148A, EP0030044, NL7908030, EP0053964, EP0031753, EP0042781 and BE706646 disclose quinoline compounds having cardiovascular, hypnotic, anticonvulsant, and antimalarial effects.

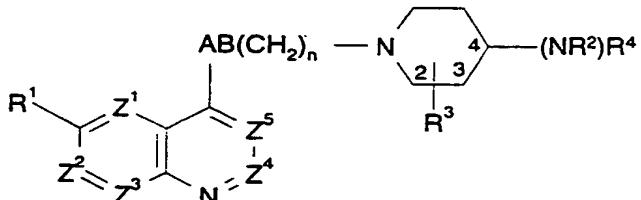
10 EP0579263, EP0742207, JP2169569, EP0296560, WO9103243, EP0449186 disclose piperidine compounds as acetylcholinesterase inhibitors and sigma receptor antagonists.

WO9802438 and WO9703069 disclose certain bicyclic heteroaromatic compounds having protein tyrosine kinase and cell proliferation inhibitor activity.

15 WO9217475, WO9802438, WO9703069 and WO9639145 disclose certain bicyclic heteroaromatic compounds having cholinesterase inhibitor, protein tyrosine kinase inhibitor, cell proliferation inhibitor and human epidermal growth factor receptor type 2 inhibitor activity.

We have now found a novel group of aminopiperidines which have antibacterial activity.

20 This invention provides a compound of formula (I) or a pharmaceutically acceptable derivative thereof:



(I)

wherein:

25 one of Z¹, Z², Z³, Z⁴ and Z⁵ is N, and the remainder are CR¹a;

R¹ and R¹a are independently hydrogen; hydroxy; (C₁₋₆)alkoxy optionally substituted by (C₁₋₆)alkoxy, amino, piperidyl, guanidino or amidino optionally N-substituted by one or 30 two (C₁₋₆)alkyl, acyl or (C₁₋₆)alkylsulphonyl groups, CONH₂, hydroxy, thiol, (C₁₋₆)alkylthio, heterocyclithio, heterocyclxy, arylthio, aryloxy, acylthio, acyloxy or (C₁₋₆)alkylsulphonyloxy; (C₁₋₆)alkoxy-substituted(C₁₋₆)alkyl; halogen; (C₁₋₆)alkyl; (C₁₋₆)alkylthio; nitro; azido; acyl; acyloxy; (C₁₋₆)alkylsulphonyl; (C₁₋₆)alkylsulphoxide;

arylsulphonyl; arylsulphoxide or an amino, piperidyl, guanidino or amidino group optionally N-substituted by one or two (C₁₋₆)alkyl, acyl or (C₁₋₆)alkylsulphonyl groups; and

5 additionally when Z⁵ is CR^{1a}, R^{1a} may be (C₁₋₄)alkyl-CO₂H or (C₁₋₄)alkyl-CONH₂ in which the C₁₋₄ alkyl is substituted by R¹²; (C₁₋₄)alkyl substituted by cyano, amino or guanidino; aminocarbonyl optionally substituted by hydroxy, (C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, aminocarbonyl(C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylsulphonyl, trifluoromethylsulphonyl, (C₁₋₆)alkenylsulphonyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl, or CH(R¹³)CO₂H or

10 CH(R¹³)CO₂NH₂ optionally further substituted by (C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, aminocarbonyl(C₁₋₆)alkyl or (C₂₋₆)alkenyl; hydroxy(C₁₋₆)alkyl; carboxy; cyano or (C₁₋₆)alkoxycarbonyl;

wherein R¹³ is a natural α -amino acid side chain or its enantiomer;

provided that when Z¹, Z², Z³, Z⁴ and Z⁵ are CR^{1a}, then R¹ is not hydrogen;

15

R² is hydrogen, or (C₁₋₄)alkyl or (C₁₋₄)alkenyl optionally substituted with 1 to 3 groups selected from:

amino optionally substituted by one or two (C₁₋₄)alkyl groups; carboxy; (C₁₋₄)alkoxycarbonyl; (C₁₋₄)alkylcarbonyl; (C₂₋₄)alkenyloxycarbonyl; (C₂₋₄)alkenylcarbonyl; aminocarbonyl wherein the amino group is optionally substituted by

hydroxy, (C₁₋₄)alkyl, hydroxy(C₁₋₄)alkyl, aminocarbonyl(C₁₋₄)alkyl, (C₂₋₄)alkenyl, (C₁₋₄)alkylsulphonyl, trifluoromethylsulphonyl, (C₁₋₄)alkenylsulphonyl, (C₁₋₄)alkoxycarbonyl, (C₁₋₄)alkylcarbonyl, (C₂₋₄)alkenyloxycarbonyl or (C₂₋₄)alkenylcarbonyl; cyano; tetrazolyl; 2-oxo-oxazolidinyl optionally substituted by R¹⁰; 3-

25 hydroxy-3-cyclobutene-1,2-dione-4-yl; 2,4-thiazolidinedione-5-yl; tetrazol-5-ylaminocarbonyl; 1,2,4-triazol-5-yl optionally substituted by R¹⁰; 5-oxo-1,2,4-oxadiazol-3-yl; thiol; halogen; (C₁₋₄)alkylthio; trifluoromethyl; azido; hydroxy optionally substituted by (C₁₋₄)alkyl, (C₂₋₄)alkenyl, (C₁₋₄)alkoxycarbonyl, (C₁₋₄)alkylcarbonyl, (C₂₋₄)alkenyloxycarbonyl, (C₂₋₄)alkenylcarbonyl; oxo; (C₁₋₄)alkylsulphonyl; (C₂₋₄)alkenylsulphonyl; or (C₁₋₄)aminosulphonyl wherein the amino group is optionally substituted by (C₁₋₄)alkyl or (C₂₋₄)alkenyl;

30 R³ is hydrogen; or
R³ is in the 2-, 3- or 4-position and is:

35 carboxy; (C₁₋₆)alkoxycarbonyl; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, aminocarbonyl(C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylsulphonyl, trifluoromethylsulphonyl, (C₁₋₆)alkenylsulphonyl, (C₁₋₆)alkyl-

6) alkoxy carbonyl, (C₁₋₆) alkyl carbonyl, (C₂₋₆) alkenyl oxycarbonyl or (C₂₋₆) alkenyl carbonyl and optionally further substituted by (C₁₋₆) alkyl, hydroxy(C₁₋₆) alkyl, aminocarbonyl(C₁₋₆) alkyl or (C₂₋₆) alkenyl; cyano; tetrazolyl; 2-oxo-oxazolidinyl optionally substituted by R¹⁰; 3-hydroxy-3-cyclobutene-1,2-dione-4-yl; 2,4-thiazolidinedione-5-yl; tetrazol-5-ylaminocarbonyl; 1,2,4-triazol-5-yl optionally substituted by R¹⁰; or 5-oxo-1,2,4-oxadiazol-3-yl; or (C₁₋₄) alkyl or ethenyl substituted with any of the substituents listed above for R³ and up to 3 groups R¹² independently selected from:

thiol; halogen; (C₁₋₆) alkylthio; trifluoromethyl; azido; (C₁₋₆) alkoxy carbonyl; (C₁₋₆) alkyl carbonyl; (C₂₋₆) alkenyl oxycarbonyl; (C₂₋₆) alkenyl carbonyl; hydroxy optionally substituted by (C₁₋₆) alkyl, (C₂₋₆) alkenyl, (C₁₋₆) alkoxy carbonyl, (C₁₋₆) alkyl carbonyl, (C₂₋₆) alkenyl oxycarbonyl, (C₂₋₆) alkenyl carbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆) alkyl, (C₂₋₆) alkenyl, (C₁₋₆) alkyl carbonyl or (C₂₋₆) alkenyl carbonyl; amino optionally mono- or disubstituted by (C₁₋₆) alkoxy carbonyl, (C₁₋₆) alkyl carbonyl, (C₂₋₆) alkenyl oxycarbonyl, (C₂₋₆) alkenyl carbonyl, (C₁₋₆) alkyl, (C₂₋₆) alkenyl, (C₁₋₆) alkylsulphonyl, (C₂₋₆) alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆) alkyl or (C₂₋₆) alkenyl; aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆) alkyl, hydroxy(C₁₋₆) alkyl, aminocarbonyl(C₁₋₆) alkyl, (C₂₋₆) alkenyl, (C₁₋₆) alkoxy carbonyl, (C₁₋₆) alkyl carbonyl, (C₂₋₆) alkenyl oxycarbonyl or (C₂₋₆) alkenyl carbonyl and optionally further substituted by (C₁₋₆) alkyl, hydroxy(C₁₋₆) alkyl, aminocarbonyl(C₁₋₆) alkyl or (C₂₋₆) alkenyl; oxo; (C₁₋₆) alkylsulphonyl; (C₂₋₆) alkenylsulphonyl; or (C₁₋₆) aminosulphonyl wherein the amino group is optionally substituted by (C₁₋₆) alkyl or (C₂₋₆) alkenyl;

25 in addition when R³ is disubstituted with a hydroxy or amino containing substituent and carboxy containing substituent these may together form a cyclic ester or amide linkage, respectively; or when R³ is in the 3- or 4-position it may with R² or R⁴ form a C₃₋₅ alkylene group optionally substituted by a group R⁵ selected from:

(C₁₋₁₂) alkyl; hydroxy(C₁₋₁₂) alkyl; (C₁₋₁₂) alkoxy(C₁₋₁₂) alkyl; (C₁₋₁₂) alkanoyloxy(C₁₋₁₂) alkyl; (C₃₋₆) cycloalkyl; hydroxy(C₃₋₆) cycloalkyl; (C₁₋₁₂) alkoxy(C₃₋₆) cycloalkyl; (C₁₋₁₂) alkanoyloxy(C₃₋₆) cycloalkyl; (C₃₋₆) cycloalkyl(C₁₋₁₂) alkyl; hydroxy-, (C₁₋₁₂) alkoxy- or (C₁₋₁₂) alkanoyloxy-(C₃₋₆) cycloalkyl(C₁₋₁₂) alkyl; cyano; cyano(C₁₋₁₂) alkyl; (C₂₋₁₂) alkenyl; (C₂₋₁₂) alkynyl; tetrahydrofuryl;

35 mono- or di-(C₁₋₁₂) alkylamino(C₁₋₁₂) alkyl; acylamino(C₁₋₁₂) alkyl; (C₁₋₁₂) alkyl- or acyl-aminocarbonyl(C₁₋₁₂) alkyl; mono- or di- (C₁₋₁₂) alkylamino(hydroxy) (C₁₋₁₂) alkyl; optionally substituted phenyl(C₁₋₁₂) alkyl, phenoxy(C₁₋₁₂) alkyl or

phenyl(hydroxy)(C₁₋₁₂)alkyl; optionally substituted diphenyl(C₁₋₁₂)alkyl; optionally substituted phenyl(C₂₋₁₂)alkenyl; optionally substituted benzoyl or benzoyl(C₁₋₁₂)alkyl; optionally substituted heteroaryl or heteroaryl(C₁₋₁₂)alkyl; and optionally substituted heteroaroyl or heteroaroyl(C₁₋₁₂)alkyl;

5

R⁴ forms a group with R³ as above defined, or is a group -CH₂-R⁵ where R⁵ is as defined above:

n is 0, 1 or 2;

10

A is NR¹¹ or CR⁶R⁷ and B is NR¹¹, O, SO₂ or CR⁸R⁹ and wherein: each of R⁶, R⁷, R⁸ and R⁹ is independently selected from: hydrogen; (C₁₋₆)alkylthio; halo; trifluoromethyl; azido; (C₁₋₆)alkyl; (C₂₋₆)alkenyl; (C₁₋₆)alkoxycarbonyl; (C₁₋₆)alkylcarbonyl; (C₂₋₆)alkenyloxycarbonyl; (C₂₋₆)alkenylcarbonyl; hydroxy, amino or 15 aminocarbonyl optionally substituted as for corresponding substituents in R³; (C₁₋₆)alkylsulphonyl; (C₂₋₆)alkenylsulphonyl; or (C₁₋₆)aminosulphonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl or (C₁₋₆)alkenyl; or R⁶ and R⁸ together represent a bond and R⁷ and R⁹ are as above defined; or R⁶ and R⁷ or R⁸ and R⁹ together represent oxo;

20

provided that:

when A is NR¹¹, B is not NR¹¹, O or SO₂;
when A is CO, B is not CO, O or SO₂;
when n is 0 and A is NR¹¹, CR⁸R⁹ can only be CO;
25 when A is CR⁶R⁷ and B is SO₂, n is 0;
when n is 0, B is not NR¹¹ or O; and
when A-B is CR⁷=CR⁹, n is 1 or 2;

R¹⁰ is selected from (C₁₋₄)alkyl; (C₂₋₄)alkenyl and aryl any of which may be optionally 30 substituted by a group R¹² as defined above; carboxy; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylsulphonyl, trifluoromethylsulphonyl, (C₁₋₆)alkenylsulphonyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl or (C₂₋₆)alkenylcarbonyl and optionally further substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl; 35 (C₁₋₆)alkylsulphonyl; trifluoromethylsulphonyl; (C₁₋₆)alkenylsulphonyl; (C₁₋₆)alkoxycarbonyl; (C₁₋₆)alkylcarbonyl; (C₂₋₆)alkenyloxycarbonyl; and (C₂₋₆)alkenylcarbonyl;

5 R^{11} is hydrogen; trifluoromethyl, (C_{1-6})alkyl; (C_{1-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{1-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{1-6})alkenyl and optionally further substituted by (C_{1-6})alkyl or (C_{1-6})alkenyl;

10 This invention also provides a method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment an effective amount of a compound of formula (I), or a pharmaceutically acceptable derivative thereof.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for use in the treatment of bacterial infections in mammals.

15 The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

Preferred groups of compounds include those where:

20 (a) Z^1 is N, and Z^2-Z^5 are CH,
(b) Z^1-Z^5 are each CH, and
(c) Z^5 is N, and Z^1-Z^4 are CH.

25 When R^1 or R^{1a} is substituted alkoxy it is preferably (C_{2-6})alkoxy substituted by optionally N-substituted amino, guanidino or amidino, or (C_{1-6})alkoxy optionally substituted by piperidyl. Suitable examples of R^1 and R^{1a} alkoxy include methoxy, n-propyloxy, iso-butyloxy, aminoethoxy, aminopropyloxy, aminobutyloxy, aminopentyloxy, guanidinopropyloxy, piperidin-4-ylmethoxy and phthalimido pentyloxy.

30 Preferably R^1 and R^{1a} are independently methoxy, amino(C_{3-5})alkyloxy, guanidino(C_{3-5})alkyloxy, piperidyl(C_{3-5})alkyloxy, nitro or fluoro; more preferably methoxy, amino(C_{3-5})alkyloxy or guanidino(C_{3-5})alkyloxy.

Z^2 and Z^4 are preferably CH.

When Z^5 is CR^{1a} , R^{1a} is preferably hydrogen, cyano, hydroxymethyl or carboxy.

35 Preferably n is 0.

R^2 is preferably hydrogen; (C_{1-4})alkyl substituted with carboxy, optionally substituted hydroxy, optionally substituted aminocarbonyl, optionally substituted amino or (C_{1-4})alkoxycarbonyl; or (C_{1-4})alkenyl substituted with (C_{1-4})alkoxycarbonyl or

carboxy. More preferred groups for R^2 are hydrogen, carboxymethyl, hydroxyethyl, aminocarbonylmethyl, ethoxycarbonylmethyl, ethoxycarbonylallyl and carboxyallyl.

Preferred examples of R^3 include hydrogen; optionally substituted aminocarbonyl; optionally substituted (C_{1-6})alkyl; carboxy(C_{1-4})alkyl; optionally substituted

5 aminocarbonyl(C_{1-4})alkyl; cyano(C_{1-4})alkyl; optionally substituted 2-oxo-oxazolidinyl and optionally substituted 2-oxo-oxazolidinyl(C_{1-4} alkyl). More preferred R^3 groups are hydrogen; $CONH_2$; 1-hydroxyalkyl e.g. CH_2OH , $CH(OH)CH_2CN$; CH_2CO_2H ; CH_2CONH_2 ; 1,2-dihydroxyalkyl e.g. $CH(OH)CH_2OH$; CH_2CN ; 2-oxo-oxazolidin-5-yl and 2-oxo-oxazolidin-5-yl(C_{1-4} alkyl).

10 R^3 is preferably in the 3- or 4-position.

In a preferred aspect, when R^3 is in the 3-position the substituents at the 3- and 4-position of the piperidine ring are *cis*.

Preferably A is $CHOH$ or NR^{11} .

Preferably B is CH_2 , SO_2 or CO .

15 Particularly preferred are those compounds where A is NH and B is CO, or A is $CHOH$ and B is CH_2 , when more preferably A is the *R*-isomer of $CHOH$.

Preferably R^{11} is hydrogen or (C_{1-4})alkyl e.g. methyl, more preferably hydrogen.

Preferably R^4 is (C_{5-12})alkyl, unsubstituted phenyl(C_{2-3})alkyl or unsubstituted phenyl(C_{3-4})alkenyl. Suitable groups R^4 include n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-dodecyl, phenylethyl, phenylpropyl or 3-phenyl-prop-2-en-yl optionally substituted on the phenyl ring; more preferably R^4 is hexyl, heptyl, 5-methylhexyl, 6-methyl heptyl or 3-phenyl-prop-2-en-yl, especially heptyl or hexyl.

25 When used herein, the term "alkyl" includes groups having straight and branched chains, for instance, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, pentyl and hexyl. The term 'alkenyl' should be interpreted accordingly.

Preferred R^5 groups are unbranched at the α and, where appropriate, β positions.

Halo or halogen includes fluoro, chloro, bromo and iodo.

30 The term "heterocyclic" as used herein includes optionally substituted aromatic and non-aromatic, single and fused, rings suitably containing up to four hetero-atoms in each ring selected from oxygen, nitrogen and sulphur, which rings may be unsubstituted or substituted by, for example, up to three groups selected from optionally substituted amino, halogen, (C_{1-6})alkyl, (C_{1-6})alkoxy, halo(C_{1-6})alkyl, hydroxy, carboxy, carboxy salts, carboxy esters such as (C_{1-6})alkoxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, aryl, and oxo groups. Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, 35 ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. Compounds within the invention containing a heterocyclyl group may occur in two or more tautomeric forms depending on the nature

of the heterocycll group; all such tautomeric forms are included within the scope of the invention.

Where an amino group forms part of a single or fused non-aromatic heterocyclic ring as defined above suitable optional substituents in such substituted amino groups include (C₁₋₆)alkyl optionally substituted by hydroxy, (C₁₋₆)alkoxy, thiol, (C₁₋₆)alkylthio, halo or trifluoromethyl, and amino-protecting groups such as acyl or (C₁₋₆)alkylsulphonyl groups.

5 The term "heteroaryl" includes the aromatic heterocyclic groups referred to above. Examples of heteroaryl groups include pyridyl, triazolyl, tetrazolyl, indolyl, 10 thienyl, isoimidazolyl, thiazolyl, furanyl, quinolinyl, imidazolidinyl and benzothienyl.

When used herein the term "aryl", includes phenyl and naphthyl.

15 Aryl groups, e.g. phenyl and benzoyl; heteroaryl and heteroaroyl groups may be optionally substituted with up to five, preferably up to three, groups selected from halogen, mercapto, (C₁₋₆)alkyl, phenyl, (C₁₋₆)alkoxy, hydroxy(C₁₋₆)alkyl, mercapto (C₁₋₆)alkyl, halo(C₁₋₆)alkyl, hydroxy, optionally substituted amino, nitro, carboxy, (C₁₋₆)alkylcarbonyloxy, (C₁₋₆)alkoxycarbonyl, formyl, and (C₁₋₆)alkylcarbonyl groups.

The term "acyl" includes formyl and (C₁₋₆)alkylcarbonyl group.

The term "acyloxy" includes (C₁₋₆)alkoxycarbonyl.

20 Some of the compounds of this invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

25 Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the 30 compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the formula (I) or pharmaceutically acceptable derivative thereof.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable derivatives.

35 Pharmaceutically acceptable derivatives include salts and esters.

Suitable pharmaceutically acceptable esters will be apparent to those skilled in the art and include for example benzyl, *p*-methoxybenzyl, benzoylmethyl, *p*-nitrobenzyl,

4-pyridylmethyl, 2,2,2-trichloroethyl, 2,2,2-tribromoethyl, *tert*-butyl, *tert*-amyl, allyl, diphenylmethyl, triphenylmethyl, adamantyl, 2-benzyloxyphenyl, 4-methylthiophenyl, tetrahydrofur-2-yl, tetrahydropyran-2-yl, pentachlorophenyl, acetonyl, *p*-toluenesulphonyl, methoxymethyl, a silyl, stannyl or phosphorus-containing group, an oxime radical of formula -N=CHRY where RY is aryl or heterocycl, or an *in vivo* hydrolysable ester radical such as defined below.

Examples of suitable *in vivo* hydrolysable ester groups include, for example, acyloxy(C₁₋₆)alkyl groups such as acetoxyethyl, pivaloyloxyethyl, α -acetoxyethyl, α -pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)prop-1-yl, and

(1-aminoethyl)carbonyloxyethyl; (C₁₋₆)alkoxycarbonyloxy(C₁₋₆)alkyl groups, such as ethoxycarbonyloxyethyl, α -ethoxycarbonyloxyethyl and propoxycarbonyloxyethyl; di(C₁₋₆)alkylamino(C₁₋₆)alkyl especially di(C₁₋₄)alkylamino(C₁₋₄)alkyl groups such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl; 2-((C₁₋₆)alkoxycarbonyl)-2-(C₂₋₆)alkenyl groups such as

15 2-(isobutoxycarbonyl)pent-2-enyl and 2-(ethoxycarbonyl)but-2-enyl; lactone groups such as phthalidyl and dimethoxyphthalidyl.

Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric, nitric or phosphoric acid; and organic acids e.g. 20 succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, *p*-toluenesulphonic, methanesulphonic or naphthalenesulphonic acid. Other salts e.g. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention.

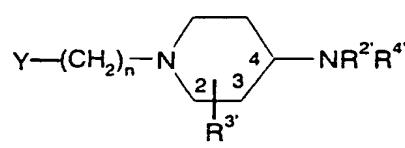
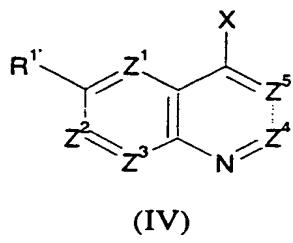
Compounds of formula (I) may also be prepared as the corresponding N-oxides.

25 Certain of the compounds of formula (I) may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention includes all such forms, in particular the pure isomeric forms. For example the invention includes compound in which an A-B group CH(OH)-CH₂ is in either isomeric configuration, the *R*-isomer is preferred. The different isomeric forms may be separated 30 or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

In a further aspect of the invention there is provided a process for preparing compounds of formula (I), and pharmaceutically acceptable derivatives thereof, which process comprises:

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reacting a compound of formula (IV) with a compound of formula (V):

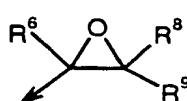


wherein Z^1, Z^2, Z^3, Z^4, Z^5 and n are as defined in formula (I); R^1', R^2', R^3' and R^4' are

5 R^1, R^2, R^3 and R^4 as defined in formula (I) or groups convertible thereto; and X and Y may be the following combinations:

- (i) X is $A'-COW$, Y is H and n is 0;
- (ii) X is $CR^6=CR^8R^9$, Y is H and n is 0;
- (iii) X is oxirane, Y is H and n is 0;
- 10 (iv) X is $N=C=O$ and Y is H ;
- (v) X is NH_2 and Y is CO_2W ;
- (vi) one of X and Y is CO_2RY and the other is CH_2CO_2RX ;
- (vii) X is CHR^6R^7 and Y is CR^8O ;
- (viii) X is $CR^6=PR^2Z_3$ and Y is CR^8O ;
- 15 (ix) X is CR^6O and Y is $CR^8=PR^2Z_3$;
- (x) one of X and Y is COW and the other is $NHR^{11'}$ or NCO ;
- (xi) X is CR^6O and Y is $NHR^{11'}$ or X is $NHR^{11'}$ and Y is CR^8O ;
- (xii) X is $NHR^{11'}$ and Y is CR^8R^9W ;
- (xiii) X is CR^6R^7W and Y is $NR^{11'}$ or O ; or
- 20 (xiv) X is $CR^6R^7SO_2W$ and Y is H and $n=0$;
- (xv) X is $NR^{11'}$ and Y is SO_2W ;

in which W is a leaving group, e.g. halogen; R^X and RY are (C_{1-6}) alkyl; R^Z is aryl or (C_{1-6}) alkyl; A' and $NR^{11'}$ are A and NR^{11} as defined in formula (I), or groups convertible thereto; and oxirane is:



wherein R^6, R^8 and R^9 are as defined in formula (I);

and thereafter optionally or as necessary converting $A', R^1', R^2', R^3', R^4'$ and $NR^{11'}$ to A , 30 R^1, R^2, R^3, R^4 and NR^{11} ; converting $A-B$ to other $A-B$, interconverting R^1, R^2, R^3 and/or R^4 , and/or forming a pharmaceutically acceptable derivative thereof.

Process variant (i) initially produces compounds of formula (I) wherein $A-B$ is $A'-CO$.

Process variant (ii) initially produces compounds of formula (I) wherein A-B is $\text{CHR}^6\text{-CR}^8\text{R}^9$.

Process variant (iii) initially produces compounds of formula (I) wherein A-B is $\text{CR}^6(\text{OH})\text{-CR}^8\text{R}^9$.

5 Process variants (iv) and (v) initially produce compounds of formula (I) where A-B is NH-CO .

Process variant (vi) initially produces compounds of formula (I) wherein A-B is CO-CH_2 or $\text{CH}_2\text{-CO}$.

10 Process variant (vii) initially produces compounds of formula (I) wherein A-B is $\text{CR}^6\text{R}^7\text{-CR}^8\text{OH}$.

Process variant (viii) and (ix) initially produce compounds of formula (I) wherein A-B is $\text{CR}^6=\text{CR}^8$.

15 Process variant (x) initially produces compounds of formula (I) where A-B is $\text{CO-NR}^{11}\text{'}$ or $\text{NR}^{11}\text{-CO}$.

Process variant (xi) initially produces compounds of formula (I) wherein A-B is $\text{CHR}^6\text{-NR}^{11}\text{'}$ or $\text{NR}^{11}\text{-CHR}^6$.

20 Process variant (xii) initially produces compounds of formula (I) wherein A-B is $\text{NR}^{11}\text{-CR}^8\text{R}^9$.

Process variant (xiii) initially produces compounds of formula (I) wherein A-B is $20 \text{ CR}^6\text{R}^7\text{-NR}^{11}\text{'}$ or $\text{CR}^6\text{R}^7\text{-O}$.

Process variant (xiv) initially produces compounds of formula (I) where A-B is $\text{CR}^6\text{R}^7\text{-SO}_2$.

25 Process variant (xv) initially produces compounds of formula (I) where A-B is $\text{NR}^{11}\text{-SO}_2$.

In process variants (i), (v) and (x) the reaction is a standard amide formation reaction involving e.g.:

1. Activation of a carboxylic acid (e.g. to an acid chloride, mixed anhydride, active ester, O-acyl-isourea or other species), and treatment with an amine (Ogliaruso, M.A.; Wolfe, J.F. in *The Chemistry of Functional Groups* (Ed. Patai, S.) *Suppl. B: The Chemistry of Acid Derivatives, Pt. I* (John Wiley and Sons, 1979), pp 442-8; Beckwith, A.L.J. in *The Chemistry of Functional Groups* (Ed. Patai, S.) *Suppl. B: The Chemistry of Amides* (Ed. Zabicky, J.) (John Wiley and Sons, 1970), p 73 ff. The acid and amide are preferably reacted in the presence of an activating agent such as 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or 1-hydroxybenzotriazole (HOBT); or

35 2. The specific methods of:

a. *in situ* conversion of an acid into the amine component by a modified Curtius reaction procedure (Shioiri, T., Murata, M., Hamada, Y., *Chem. Pharm. Bull.* 1987, 35, 2698)

b. *in situ* conversion of the acid component into the acid chloride under neutral conditions (Villeneuve, G. B.; Chan, T. H., *Tetrahedron Lett.* 1997, 38, 6489).

The process variant (ii) is a standard addition reaction using methods well known to those skilled in the art. The process is preferably carried out in a polar organic solvent e.g. acetonitrile in the presence of an organic base e.g. triethylamine.

In process variant (iii) the coupling may be effected in acetonitrile at room temperature in the presence of one equivalent of lithium perchlorate as catalyst (general method of J.E. Chateauneuf *et al.*, *J. Org. Chem.*, 56, 5939-5942, 1991). In some cases an elevated temperature such as 40 – 70 °C may be beneficial. Alternatively, the piperazine may be treated with a base, such as one equivalent of butyl lithium, and the resulting salt reacted with the oxirane in an inert solvent such as tetrahydrofuran, preferably at an elevated temperature such as 80°C. Use of a chiral epoxide will afford single diastereomers. Alternatively, mixtures of diastereomers may be separated by preparative HPLC or by conventional resolution through crystallisation of salts formed from chiral acids.

The process variant (iv) is a standard urea formation reaction from the reaction of an isocyanate with an amine and is conducted by methods well known to those skilled in the art (for example see March, J; *Advanced Organic Chemistry, Edition 3* (John Wiley and Sons, 1985), p802-3). The process is preferably carried out in a polar solvent such as N,N-dimethylformamide

In process variant (vi) the process is two step: firstly a condensation using a base, preferably sodium hydride or alkoxide, sodamide, alkyl lithium or lithium dialkylamide, preferably in an aprotic solvent e.g. ether, THF or benzene; secondly, hydrolysis using an inorganic acid, preferably HCl in aqueous organic solvent at 0-100°C. Analogous routes are described in DE330945, EP31753, EP53964 and H. Sargent, *J. Am. Chem. Soc.* **68**, 2688-2692 (1946). Similar Claisen methodology is described in Soszko *et. al.*, *Pr.Kom.Mat. Przr.Poznan.Tow.Przyj.Nauk.*, (1962), 10, 15.

In process variant (vii) the reaction is carried out in the presence of a base, preferably organometallic or metal hydride e.g. NaH, lithium diisopropylamide or NaOEt, preferably in an aprotic solvent, preferably THF, ether or benzene at -78 to 25°C (analogous process in Gutswiller *et al.* (1978) *JACS* 100, 576).

In process variants (viii) and (ix) if a base is used it is preferably NaH, KH, an alkyl lithium e.g. BuLi, a metal alkoxide e.g. NaOEt, sodamide or lithium dialkylamide e.g. di-isopropylamide. An analogous method is described in US 3989691 and M.Gates *et. al.* (1970) *J. Amer.Chem.Soc.*, 92, 205, as well as Taylor *et al.* (1972) *JACS* 94, 6218.

In process variant (xi) where X or Y is CHO the reaction is a standard reductive alkylation using, e.g., sodium triacetoxyborohydride (Gribble, G. W. in *Encyclopedia of Reagents for Organic Synthesis* (Ed. Paquette, L. A.) (John Wiley and Sons, 1995), p 4649).

5 The process variants (xii) and (xiii) are standard alkylation reactions well known to those skilled in the art, for example where an alcohol or amine is treated with an alkyl halide in the presence of a base (for example see March, J; *Advanced Organic Chemistry*, Edition 3 (John Wiley and Sons, 1985), p364-366 and p342-343). The process is preferably carried out in a polar solvent such as N,N-dimethylformamide

10 In process variant (xiv) and (xv) the reaction is a standard sulphonamide formation reaction well known to those skilled in the art. This may be e.g. the reaction of a sulphonyl halide with an amine.

15 Reduction of a carbonyl group B to CHOH can be readily accomplished using reducing agents well known to those skilled in the art, e.g. sodium borohydride in aqueous ethanol or lithium aluminium hydride in ethereal solution. This is analogous to methods described in EP53964, US384556 and J. Gutzwiller *et al*, *J. Amer. Chem. Soc.*, 1978, 100, 576.

20 The carbonyl group B may be reduced to CH₂ by treatment with a reducing agent such as hydrazine in ethylene glycol, at e.g. 130-160°C, in the presence of potassium hydroxide.

Reaction of a carbonyl group B with an organometallic reagent yields a group where R⁸ is OH and R⁹ is alkyl.

25 A hydroxy group on A or B may be oxidised to a carbonyl group by oxidants well known to those skilled in the art, for example, manganese dioxide, pyridinium chlorochromate or pyridinium dichromate.

A hydroxyalkyl A-B group CHR⁶CR⁸OH or CR⁶(OH)CHR⁸ may be dehydrated to give the group CR⁶=CR⁸ by treatment with an acid anhydride such as acetic anhydride.

30 Methods for conversion of CR⁶=CR⁸ by reduction to CHR⁶CHR⁸ are well known to those skilled in the art, for example using hydrogenation over palladium on carbon as catalyst. Methods for conversion of CR⁶=CR⁸ to give the A-B group CR⁶(OH)CHR⁸ or CHR⁶CR⁸OH are well known to those skilled in the art for example by epoxidation and subsequent reduction by metal hydrides, hydration, hydroboration or oxymercuration.

35 An amide carbonyl group may be reduced to the corresponding amine using a reducing agent such as lithium aluminium hydride.

A hydroxy group in A or B may be converted to azido by activation and displacement e.g. under Mitsunobu conditions using hydrazoic acid or by treatment with

diphenylphosphorylazide and base, and the azido group in turn may be reduced to amino by hydrogenation.

R¹, R², R³ and R⁴ are preferably R¹, R², R³ and R⁴. R¹ is preferably methoxy. R² is preferably hydrogen. R³ is preferably hydrogen, CONH₂, CH₂OH, CH₂CO₂H, CH₂CONH₂, CH(OH)CH₂OH, CH(OH)CH₂CN, CH₂CN, 2-oxo-oxazolidin-5-yl and 2-oxo-oxazolidin-5-yl(C₁₋₄alkyl). R⁴ is preferably heptyl.

Conversions of R¹, R², R³ and R⁴ and interconversions of R¹, R², R³ and R⁴ are conventional. In compounds which contain an optionally protected hydroxy group, suitable conventional hydroxy protecting groups which may be removed without 10 disrupting the remainder of the molecule include acyl and alkylsilyl groups.

For example R¹ methoxy is convertible to R¹ hydroxy by treatment with lithium and diphenylphosphine (general method described in Ireland *et al*, *J. Amer. Chem. Soc.*, 1973, 7829) or HBr. Alkylation of the hydroxy group with a suitable alkyl derivative bearing a leaving group such as halide and a protected amino, piperidyl, amidino or 15 guanidino group or group convertible thereto, yields, after conversion/deprotection, R¹ alkoxy substituted by optionally N-substituted amino, piperidyl, guanidino or amidino.

R³ alkenyl is convertible to hydroxyalkyl by hydroboration using a suitable reagent such as 9-borabicyclo[3.3.1]nonane, epoxidation and reduction or oxymercuration.

20 R³ 1,2-dihydroxyalkyl can be prepared from R³ alkenyl using osmium tetroxide or other reagents well known to those skilled in the art (see Advanced Organic Chemistry, *Ed. March, J.*, John Wiley and Sons, 1985, p 732-737 and refs. cited therein) or epoxidation followed by hydrolysis (see Advanced Organic Chemistry, *Ed. March, J.*, John Wiley and Sons, 1985, p 332,333 and refs. cited therein).

25 R³ vinyl can be chain extended by standard homologation, e.g. by conversion to hydroxyethyl followed by oxidation to the aldehyde, which is then subjected to a Wittig reaction.

Opening an epoxide-containing R³ group with cyanide anion yields a CH(OH)-CH₂CN group.

30 Opening an epoxide-containing R³ group with azide anion yields an azide derivative which can be reduced to the amine. Conversion of the amine to a carbamate is followed by ring closure with base to give the 2-oxo-oxazolidinyl containing R³ group.

Substituted 2-oxo-oxazolidinyl containing R³ groups may be prepared from the corresponding aldehyde by conventional reaction with a glycine anion equivalent, 35 followed by cyclisation of the resulting amino alcohol (M Grauert *et al*, *Ann. Chem.*, 1985, 1817; Rozenberg *et al*, *Angew. Chem. Int. Ed. Engl.*, 1994, 33(1), 91). The

resulting 2-oxo-oxazolidinyl group contains a carboxy group which can be converted to other R¹⁰ groups by standard procedures.

Carboxy groups within R³ may be prepared by Jones' oxidation of the corresponding alcohols CH₂OH using chromium acid and sulphuric acid in water/methanol (E.R.H. Jones *et al*, *J. Chem. Soc.*, 1946, 39). Other oxidising agents may be used for this transformation such as sodium periodate catalysed by ruthenium trichloride (G.F. Tutwiler *et al*, *J. Med. Chem.*, 1987, 30(6), 1094), chromium trioxide-pyridine (G. Just *et al*, *Synth. Commun.*, 1979, 9(7), 613), potassium permanganate (D.E. Reedich *et al*, *J. Org. Chem.*, 1985, 50(19), 3535), and pyridinium chlorochromate (D. Askin *et al*, *Tetrahedron Lett.*, 1988, 29(3), 277).

Other routes to the synthesis of carboxy groups within R³ are well known to those skilled in the art.

R³ groups containing a cyano group may be prepared by conversion of an alcohol to a suitable leaving group such as the corresponding tosylate by reaction with para-toluenesulphonyl chloride (M.R. Bell, *J. Med. Chem.*, 1970, 13, 389), or the iodide using triphenylphosphine, iodine, and imidazole (G. Lange, *Synth. Commun.*, 1990, 20, 1473). The second stage is the displacement of the leaving group with cyanide anion (L.A. Paquette *et al*, *J. Org. Chem.*, 1979, 44(25), 4603; P.A. Grieco *et al*, *J. Org. Chem.*, 1988, 53(16), 3658).

Other functional groups in R³ may be obtained by conventional conversions of carboxy or cyano groups.

Tetrazoles are conveniently prepared by reaction of sodium azide with the cyano group (e.g. F. Thomas *et al*, *Bioorg. Med. Chem. Lett.*, 1996, 6(6), 631; K. Kubo *et al*, *J. Med. Chem.*, 1993, 36, 2182) or by reaction of azidotri-n-butyl stannane with the cyano group followed by acidic hydrolysis (P.L. Ornstein, *J. Org. Chem.*, 1994, 59, 7682 and *J. Med. Chem.*, 1996, 39(11), 2219).

The 3-hydroxy-3-cyclobutene-1,2-dion-4-yl group (e.g. R.M. Soll, *Bioorg. Med. Chem. Lett.*, 1993, 3(4), 757 and W.A. Kinney, *J. Med. Chem.*, 1992, 35(25), 4720) can be prepared by the following sequence:- (1) a compound where R³ is (CH₂)_nCHO (n = 0,1,2) is treated with triethylamine, carbontetrabromide-triphenylphosphine to give initially (CH₂)_nCH=CHBr; (2) dehydrobromination of this intermediate to give the corresponding bromoethyne derivative (CH₂)_nC≡CBr (for this 2 stage sequence see D. Grandjean *et al*, *Tetrahedron Lett.*, 1994, 35(21), 3529); (3) palladium-catalysed coupling of the bromoethyne with 4-(1-methylethoxy)-3-(tri-n-butylstannyl)cyclobut-3-ene-1,2-dione (Liebeskind *et al*, *J. Org. Chem.*, 1990, 55, 5359); (4) reduction of the ethyne moiety to -CH₂CH₂- under standard conditions of hydrogen and palladium on charcoal catalysis (see Howard *et al*, *Tetrahedron*, 1980, 36, 171); and finally (4) acidic hydrolysis

of the methylethoxyester to generate the corresponding 3-hydroxy-3-cyclobutene-1,2-dione group (R.M. Soll, *Bioorg. Med. Chem. Lett.*, 1993, 3(4), 757).

The tetrazol-5-ylaminocarbonyl group may be prepared from the corresponding carboxylic acid and 2-aminotetrazole by dehydration with standard peptide coupling agents such as 1,1'-carbonyldiimidazole (P.L. Ornstein *et al*, *J. Med Chem.*, 1996, 39(11), 2232).

The alkyl- and alkenyl-sulphonylcarboxamides are similarly prepared from the corresponding carboxylic acid and the alkyl- or alkenyl-sulphonamide by dehydration with standard peptide coupling agents such as 1,1'-carbonyldiimidazole (P.L. Ornstein *et al*, *J. Med. Chem.*, 1996, 39(11), 2232).

The hydroxamic acid groups are prepared from the corresponding acids by standard amide coupling reactions e.g. N.R. Patel *et al*, *Tetrahedron*, 1987, 43(22), 5375.

2,4-Thiazolidinedione groups may be prepared from the aldehydes by condensation with 2,4-thiazolidinedione and subsequent removal of the olefinic double bond by hydrogenation.

The preparation of 5-oxo-1,2,4-oxadiazoles from nitriles is described by Y. Kohara *et al*, *Bioorg. Med. Chem. Lett.*, 1995, 5(17), 1903.

1,2,4-Triazol-5-yl groups may be prepared from the corresponding nitrile by reaction with an alcohol under acid conditions followed by reaction with hydrazine and then an R¹⁰-substituted activated carboxylic acid (see J.B. Polya in "Comprehensive Heterocyclic Chemistry" Edition 1, p762, Ed A.R. Katritzky and C.W. Rees, Pergamon Press, Oxford, 1984 and J.J. Ares *et al*, *J. Heterocyclic Chem.*, 1991, 28(5), 1197).

Other substituents on R³ alkyl or alkenyl may be interconverted by conventional methods, for example hydroxy may be derivatised by esterification, acylation or etherification. Hydroxy groups may be converted to halogen, thiol, alkylthio, azido, alkylcarbonyl, amino, aminocarbonyl, oxo, alkylsulphonyl, alkenylsulphonyl or aminosulphonyl by conversion to a leaving group and substitution by the required group or oxidation as appropriate or reaction with an activated acid, isocyanate or alkoxyisocyanate. Primary and secondary hydroxy groups can be oxidised to an aldehyde or ketone respectively and alkylated with a suitable agent such as an organometallic reagent to give a secondary or tertiary alcohol as appropriate.

Compounds of formula (I) where R² and R³ are a divalent residue =CR⁵¹R⁶¹ can be prepared by treatment of a compound of formula (I) where R³ is alken-1-yl with a strong base in an aprotic solvent. Suitable bases include Ph₂PLi/PhLi (as described in Ireland *et al*, *J. Amer. Chem. Soc.*, 1973, 7829), *t*-BuLi, and suitable solvents include THF and ether.

NH is converted to NR⁴ by conventional means such as alkylation with an alkyl halide in the presence of base, acylation/reduction or reductive alkylation with an aldehyde.

It will be appreciated that under certain circumstances interconversions may 5 interfere, for example, A or B hydroxy groups in A or B and the piperidine NH will require protection e.g. as a carboxy- or silyl-ester group for hydroxy and as an acyl derivative for piperidine nitrogen, during conversion of R¹, R², R³ or R⁴.

Compounds of formula (IV) where X is CR⁶R⁷SO₂W may be prepared by a route 10 analogous to that of Ahmed El Hadri *et al.*, *J. Heterocyclic Chem.*, 1993, 30(3), 631. Thus compounds of formula (IV) where X is CH₂SO₂OH may be prepared by reacting the corresponding 4-methyl compound with N-bromosuccinimide, followed by treatment with sodium sulfite. The leaving group W may be converted to another leaving group W, e.g. a halogen group, by conventional methods.

The isocyanate of formula (IV) may be prepared conventionally from a 4-amino 15 derivative such as 4-amino-quinoline, and phosgene, or phosgene equivalent (eg triphosgene) or it may be prepared more conveniently from a 4-carboxylic acid by a 'one-pot' Curtius Reaction with diphenyl phosphoryl azide (DPPA) [see T. Shiori *et al.* *Chem. Pharm. Bull.* 35, 2698-2704 (1987)].

The 4-amino derivatives are commercially available or may be prepared by 20 conventional procedures from a corresponding 4-chloro derivative by treatment with ammonia (O.G. Backeberg *et. al.*, *J. Chem Soc.*, 381, 1942.) or propylamine hydrochloride (R. Radinov *et. al.*, *Synthesis*, 886, 1986).

4-Alkenyl compounds of formula (IV) may be prepared by conventional 25 procedures from a corresponding 4-halogeno-derivative by e.g. a Heck synthesis as described in e.g. *Organic Reactions*, 1982, 27, 345.

4-Halogeno derivatives of compounds of formula (IV) are commercially available, or may be prepared by methods known to those skilled in the art. A 4-chloroquinoline is prepared from the corresponding quinolin-4-one by reaction with phosphorus oxychloride (POCl₃) or phosphorus pentachloride, PCl₅. A 4-chloroquinazoline is prepared from the 30 corresponding quinazolin-4-one by reaction with phosphorus oxychloride (POCl₃) or phosphorus pentachloride, PCl₅. A quinazolinone and quinazolines may be prepared by standard routes as described by T.A. Williamson in *Heterocyclic Compounds*, 6, 324 (1957) Ed. R.C. Elderfield.

4-Carboxy derivatives of compounds of formula (IV) are commercially available 35 or may be prepared by conventional procedures for preparation of carboxy heteroaromatics well known to those skilled in the art. For example, quinazolines may be prepared by standard routes as described by T.A. Williamson in *Heterocyclic Compounds*,

6, 324 (1957) Ed. R.C. Elderfield. Pyridazines and naphthyridines may be prepared by routes analogous to those described in *Comprehensive Heterocyclic Chemistry*, Volumes 2 & 3, Ed A.J. Boulton and A. McKillop. These 4-carboxy derivatives may be activated by conventional means, e.g. by conversion to an acyl halide or anhydride.

5 A 4-oxirane derivative of compounds of formula (IV) is conveniently prepared from the 4-carboxylic acid by first conversion to the acid chloride with oxalyl chloride and then reaction with trimethylsilyldiazomethane to give the diazoketone derivative. Subsequent reaction with 5M hydrochloric acid gives the chloromethylketone. Reduction with sodium borohydride in aqueous methanol gives the chlorohydrin which undergoes 10 ring closure to afford the epoxide on treatment with base, e.g. potassium hydroxide in ethanol-tetrahydrofuran.

If a chiral reducing agent such as (+) or (-)-B-chlorodiisopinocamphenylborane [DIP-chloride] is substituted for sodium borohydride, the prochiral chloromethylketone is converted into the chiral chlorohydrin with ee values generally 85-95% [see C. Bolm *et al.*, *Chem. Ber.* 125, 1169-1190, (1992)]. Recrystallisation of the chiral epoxide gives material in the mother liquor with enhanced optical purity (typically ee 95%).

The (R)-epoxide, when reacted with a piperazine derivative gives ethanolamine compounds as single diastereomers with (R)-stereochemistry at the benzylic position.

Alternatively, the epoxide may be prepared from the 4-carboxaldehyde by a Wittig 20 approach using trimethylsulfonium iodide [see G.A. Epling and K-Y Lin, *J. Het. Chem.*, 1987, 24, 853-857], or by epoxidation of a 4-vinyl derivative.

4-Hydroxy-1,5-naphthyridines can be prepared from 3-aminopyridine derivatives by reaction with ethoxymethylenemalonic ester to produce the 4-hydroxy-3-carboxylic acid ester derivative with subsequent hydrolysis to the acid, followed by thermal 25 decarboxylation in quinoline (as for example described for 4-Hydroxy-[1,5]naphthyridine-3-carboxylic acid, Joe T. Adams *et al.*, *J.Amer.Chem.Soc.*, 1946, **68**, 1317. A 4-hydroxy-[1,5]naphthyridine can be converted to the 4-chloro derivative by heating in phosphorus oxychloride. A 4-amino 1,5-naphthyridine can be obtained from the 4-chloro derivative by reaction with n-propylamine in pyridine.

30 Similarly, 6-methoxy-1,5-naphthyridine derivatives can be prepared from 3-amino-6-methoxypyridine.

1,5-Naphthyridines may be prepared by other methods well known to those skilled in the art (for examples see P.A. Lowe in "Comprehensive Heterocyclic Chemistry" Volume 2, p581-627, Ed A.R. Katritzky and C.W. Rees, Pergamon Press, Oxford, 1984).

35 For compounds of formula (V), suitable amines may be prepared from the corresponding 4-substituted piperidine acid or alcohol. In a first instance, an N-protected piperidine containing an acid bearing substituent, can undergo a Curtius rearrangement

and the intermediate isocyanate can be converted to a carbamate by reaction with an alcohol. Conversion to the amine may be achieved by standard methods well known to those skilled in the art used for amine protecting group removal. For example, an acid substituted N-protected piperidine can undergo a Curtius rearrangement e.g. on treatment

5 with diphenylphosphoryl azide and heating, and the intermediate isocyanate reacts in the presence of 2-trimethylsilylethanol to give the trimethylsilylethylcarbamate (T.L. Capson & C.D. Poulter, *Tetrahedron Lett.*, 1984, 25, 3515). This undergoes cleavage on treatment with tetrabutylammonium fluoride to give the 4-amine substituted N-protected piperidine.

10 In a second instance, an N-protected piperidine containing an alcohol bearing substituent undergoes a Mitsunobu reaction (for example as reviewed in Mitsunobu, *Synthesis*, (1981), 1), for example with succinimide in the presence of diethyl azodicarboxylate and triphenylphosphine to give the phthalimidoethylpiperidine.

15 Removal of the phthaloyl group, for example by treatment with methylhydrazine, gives the amine of formula (V).

Conversions of R¹, R², R³ and R⁴ may be carried out on the intermediates of formulae (IV), and (V) prior to their reaction to produce compounds of formula (I) in the same way as described above for conversions after their reaction.

20 Further details for the preparation of compounds of formula (I) are found in the examples.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds of formula (I). Libraries of compounds of formula (I) may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either

25 solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I) or pharmaceutically acceptable derivatives thereof.

30 Novel intermediates of formulae (IV) and (V) are also part of this invention.

30 The antibacterial compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibacterials.

35 The pharmaceutical compositions of the invention include those in a form adapted for oral, topical or parenteral use and may be used for the treatment of bacterial infection in mammals including humans.

The composition may be formulated for administration by any route. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

5 The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

10 The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

15 Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

20 30 Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

25 For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

35 Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be

frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to 1.5 to 50 mg/kg per day.

15 Suitably the dosage is from 5 to 20 mg/kg per day.

No toxicological effects are indicated when a compound of formula (I) or a pharmaceutically acceptable derivative thereof is administered in the above-mentioned dosage range.

20 The compound of formula (I) may be the sole therapeutic agent in the compositions of the invention or a combination with other antibacterials. If the other antibacterial is a β -lactam then a β -lactamase inhibitor may also be employed.

Compounds of formula (I) are active against a wide range of organisms including both Gram-negative and Gram-positive organisms.

25 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

30 The following examples illustrate the preparation of certain compounds of formula (I) and the activity of certain compounds of formula (I) against various bacterial organisms.

EXAMPLES

Example 1. cis-3-(R/S)-Ethoxycarbonyl-4-(S/R)-heptylamino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate Example 1. cis-3-(R/S)-

5 **Ethoxycarbonyl-4-(S/R)-heptylamino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate**

(a) [R]-2-(6-Methoxyquinolin-4-yl)oxirane

A solution of 6-methoxyquinoline-4-carboxylic acid (10g) in dichloromethane
10 was heated under reflux with oxalyl chloride (5ml) and dimethylformamide (2 drops) for 1 hour and evaporated to dryness. The residue, in dichloromethane (100ml) was treated with a 2M solution of trimethylsilyldiazomethane in hexane (50ml) and stirred at room temperature for 18 hours. 5M Hydrochloric acid (150ml) was added and the solution was stirred at room temperature for 3 hours. It was basified with sodium carbonate solution, 15 extracted with ethyl acetate and chromatographed on silica gel eluting with ethyl acetate-hexane to give the chloromethyl ketone (4.2g). A batch of the chloromethyl ketone (20g) was reduced with (+)-B-chlorodiisopinocampheylborane (40g) in dichloromethane (400ml) at room temperature for 18 hours followed by treatment with diethanolamine (30 g) for 3 hours. The product was chromatographed on silica gel eluting with ethyl acetate-hexane to give the chloroalcohol (16.8g), which was dissolved in tetrahydrofuran (100 ml) and reacted with sodium hydroxide (2.6g) in water (13ml) for 1.5 hours. The reaction mixture was evaporated to dryness and chromatographed on silica gel eluting with ethyl acetate - hexane to give the title compound as a solid (10.4 g) (84% ee by chiral HPLC). Recrystallisation from ether-pentane gave mother-liquor (7.0 g) (90% ee).

20 25 MS (+ve ion electrospray) m/z 202 (MH+)

The absolute stereochemistry was defined to be (R) by an NMR study on the Mosher's esters derived from the product obtained by reaction with 1-t-butylpiperazine.

(b) 1-tert-Butoxycarbonyl-3-ethoxycarbonyl-4-heptylamino-1,2,5,6-tetrahydropyridine

A solution of 1-tert-butoxycarbonyl-3-ethoxycarbonyl-piperidin-4-one (prepared
30 from 3-ethoxycarbonyl-piperidin-4-one and di-tert-butyl-dicarbonate in dichloromethane and triethylamine) (8.5g) and heptylamine (3.61g) in toluene (100ml) was heated under reflux in a Dean and Stark apparatus for 18 hours and then evaporated to dryness to give an oil.

(c) cis-1-tert-Butoxycarbonyl-3-(R/S)-ethoxycarbonyl-4-(S/R)-heptylamino-piperidine

35 The enamine (1b) in ethanol (100ml) was hydrogenated at 50psi (Parr reaction vessel) over 10% palladium-carbon (2g) for 48 hours, filtered and evaporated to dryness

to give an oil. The product was chromatographed on silica gel (ethyl acetate -hexane) to afford the title compound (4.5g), as an oil.

MS (+ve ion electrospray) m/z 371 (MH⁺).

(d) *cis*-3-(R/S)-Ethoxycarbonyl-4-(S/R)-heptylamino-piperidine

5 The amine (1c) (1.2g) was treated with dichloromethane (30ml) and trifluoroacetic acid (30ml) at room temperature for 3.5 hours and evaporated to dryness. It was basified with sodium carbonate solution, extracted with dichloromethane, dried over sodium sulfate and evaporated to afford an oil (0.9g).

(e) Title compound

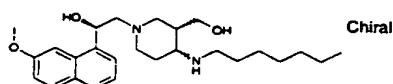
10 A solution of [R]-2-(6-methoxyquinolin-4-yl)oxirane (1a) (0.626g) and the piperidine (1d) (0.85g) in acetonitrile (5ml) containing lithium perchlorate (0.332g) was stirred at room temperature for 15 hours and evaporated to dryness. The product was dissolved in dichloromethane, washed with sodium carbonate, dried over sodium sulfate, and chromatographed on silica gel (ethyl acetate-hexane) to afford the title compound

15 (0.69g) as the oily free base.

MS (+ve ion electrospray) m/z 472 (MH⁺).

The free base was treated with 2 molar equivalents of oxalic acid in ether and the resulting solid was collected, triturated with ether, to afford the dioxalate salt as a white solid.

20 **Example 2. *cis*-4-(S/R)-Heptylamino-3-(R/S)-hydroxymethyl-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate**



25 The ester Example (1) (0.105g) in dry tetrahydrofuran (5ml) at -10°C was treated with lithium aluminium hydride (0.27ml of a 1M solution in ether) for 3 hours and then quenched by the addition of 2M sodium hydroxide. Dichloromethane and sodium sulfate were added and the solution was filtered and evaporated to dryness. The product was chromatographed on silica gel (methanol-dichloromethane) to afford the title compound

30 (0.057g), as the oily free base.

MS (+ve ion electrospray) m/z 430 (MH⁺).

¹H NMR (CDCl₃) δ: 0.88 (3H, t), 1.30 (9H, bs), 1.47 (2H, bs), 1.75 (1H, bt), 1.95-2.80 (-8H, m), 2.98 (2H, m), 3.85 (1H, m), 3.95 (3H, s), 4.25 (1H, bt), 5.41 (1H, m) 7.17 (1H, bs), 7.39 (1H, dd), 7.65 (1H, d), 8.05 (1H, d), 8.78 (1H, d).

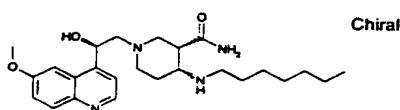
35 The free base in dichloromethane-ether was converted to the dioxalate salt in the normal manner, affording a white solid.

Example 3. cis-3-(R/S)-Carboxy-4-(S/R)-heptylamino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine trihydrochloride

5 The ester Example (1) (0.07g) was heated in 2M hydrochloric acid (7ml) under reflux for 5 hours and then evaporated to dryness to give the title compound as a foam. MS (+ve ion electrospray) m/z 444 (MH⁺).

Example 4. cis-3-(R/S)-Aminocarbonyl-4-(S/R)-heptylamino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate

10



The ester Example (1) (0.18g) in methanol (3ml) was heated with ammonia (3ml) and sodium cyanide (5mg) at 50°C (sealed bomb) for 4 days and evaporated to dryness.

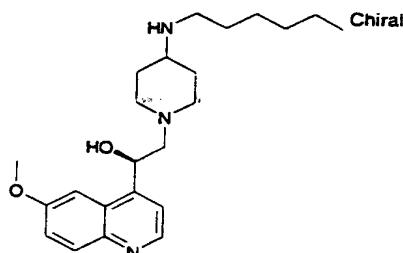
15 Chromatography on silica gel (ethyl-acetate then methanol-dichloromethane) gave the title compound (0.046g), as the free base.

MS (+ve ion electrospray) m/z 443 (MH⁺).

The free base in dichloromethane-ether was converted to the dioxalate salt in the normal manner, affording a white solid.

20

Example 5. 4-Hexylamino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine oxalate



25

(a) 4-(1,3-Dioxolan-2-yl)-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine.

[R]-2-(6-Methoxyquinolin-4-yl)oxirane (1a) (470 mg) and 1,4-dioxa-8-azaspiro-[4,5]-decane (0.33 ml) were dissolved in dry dichloromethane (5 ml) and ytterbium triflate (30 mol%) was added. The mixture was stirred for 6 hours, filtered through celite, 30 evaporated and chromatographed on silica gel (dichloromethane then methanol-dichloromethane) to afford the title compound (690 mg).

MS (+ve ion electrospray) m/z 345 (MH⁺).

(b) 4-Oxo-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine.

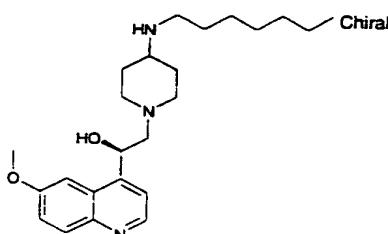
The acetal (5a) was cleaved by treatment with 5M HCl (10 ml) in acetone (20 ml) at 60 °C overnight. The mixture was basified with sodium bicarbonate solution and concentrated. Extraction into dichloromethane, evaporation and chromatography on silica gel (dichloromethane then methanol-dichloromethane) gave a yellow gum (482 mg).

5 (c) Title compound

The ketone (5b) (159 mg) was treated with hexylamine (0.12 ml) in methanol for 1 hour and sodium triacetoxyborohydride (170 mg) was added. The mixture was stirred 10 for 4 hours, evaporated, and the residue partitioned between dichloromethane/water. The dichloromethane extract was evaporated and chromatographed on silica gel (dichloromethane then methanol-dichloromethane) to give a colourless oil as the free base (150 mg) which was converted to the dioxalate salt in the normal manner, affording a white solid.

15 MS (+ve ion electrospray) m/z 386 (MH⁺).

Example 6. 4-Heptylamino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate



20

The title compound was prepared from the ketone (5b) as described in Example (5c), using heptylamine.

MS (+ve ion electrospray) m/z 400 (MH⁺).

25

Example 7. 4-Heptylamino-1-[2-(S)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate

(a) [S]-2-(6-Methoxyquinolin-4-yl)oxirane

This was prepared by the method of Example (1a) except that the chloromethylketone was reduced with (-)-B-chlorodiisopinocampheylborane. The product had 90% ee.

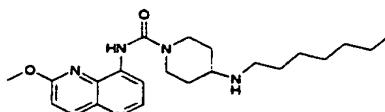
30 MS (+ve ion electrospray) m/z 202 (MH⁺).

(b) Title compound

The title compound was prepared from [S]-2-(6-methoxyquinolin-4-yl)oxirane (7a) as described in Example (5) using heptylamine.

MS (+ve ion electrospray) m/z 400 (MH⁺).

5 **Example 8. 4-Heptylamo-1-(6-methoxy-[1,5]-naphthyridin-4-yl)aminocarbonylpiperidine**



10 (a) 4-Hydroxy-6-methoxy-[1,5]naphthyridine-3-carboxylic acid ethyl ester
3-Amino-6-methoxypyridine (12.41 g) and diethyl ethoxymethylene malonate (20.2 ml) in Dowtherm A (400 ml) were heated at reflux, under argon for 1 hour. The cooled reaction mixture was poured into pentane (1 litre). The precipitated solid was collected by filtration, washed with pentane and dried to afford a solid (24.78 g, crude).

15 MS (+ve ion electrospray) m/z 249 (MH⁺).
(b) 4-Hydroxy-6-methoxy-[1,5]naphthyridine-3-carboxylic acid
The ester (8a) (0.642g) in 10% aqueous sodium hydroxide (115 ml) was heated at reflux for 1.5 hours. The reaction mixture was cooled then acidified with glacial acetic acid. The precipitated solid was collected by filtration, washed with water and dried *in vacuo* to afford a beige solid (0.542g).

20 MS (+ve ion electrospray) m/z 221 (MH⁺).
(c) 4-Chloro-6-methoxy-[1,5]naphthyridine

25 The acid (8b) (6.82 g) was heated in quinoline (20ml) at reflux for 2 hours, the mixture was cooled and poured into ether (200ml) and the orange solid was filtered and washed with ether (5 x 200ml). A sample (3.87g) of the dried solid was treated with phosphorus oxychloride (30ml) at room temp for 3 hours, the solvent was removed *in vacuo* and the residue quenched with crushed ice (200g). The mixture was basified with ammonia solution and filtered. The solid was washed with dichloromethane (10 x 100ml), which was evaporated and chromatographed on silica gel (dichloromethane as eluent) to give a yellow solid (3.0g).

30 MS (+ve ion electrospray) m/z 195, 197 (MH⁺).
(d) 4-Amino-6-methoxy-[1,5]naphthyridine

35 A solution of the chloro compound (8c) (2.0g) in pyridine (30ml) was treated with n-propylamine hydrochloride (6.0g) and the mixture heated at reflux for 16 hours. The reaction mixture was cooled and partitioned between water and ethyl acetate. The aqueous phase was washed with ethyl acetate, the combined organics dried (Na₂SO₄) and

the solvent removed under reduced pressure. Purification by chromatography on silica gel (5-10% methanol in dichloromethane) afforded a yellow solid (1.0g).

¹H NMR (CDCl₃) δ: 4.05 (3H, s), 5.36 (2H, bs), 6.71 (1H, d, J=5 Hz), 7.08 (1H, d, J=9Hz), 8.10 (1H, d, J=9Hz), 8.40 (1H, d, J=5Hz).

5 MS (+ve ion electrospray) m/z: 176 (MH⁺).

(e) 4-Oxo-1-(6-methoxy-[1,5]-naphthyridin-4-yl)aminocarbonylpiperidine, ethylene ketal

A solution of the amine (8d) (0.32g, 2 mmol) in chloroform (6 ml) was treated with N,N-dimethylaminopyridine (0.24g, 2 mmol) then 1,1'-carbonyldiimidazole (0.42g, 2.6 mmol). After 2 hours the chloroform was removed by evaporation and the residue treated with a solution of 4-oxopiperidine, ethylene ketal (0.31g, 0.22mmol) in N,N-dimethylformamide (5 ml). The mixture was heated at 100°C for 1 hour, then partitioned between ethyl acetate and dilute brine. The organic extract was washed with water (3x), brine, dried and evaporated to give a yellow solid (0.8g). Chromatography on silica gave the product as a white solid (0.47g, 71%).

10 15 MS (+ve ion electrospray) m/z 345 (MH⁺).

(f) 4-Oxo-1-(6-methoxy-1,5-naphthyridin-4-yl)aminocarbonylpiperidine

A solution of Example (8e) (0.46g, 1.4 mmol) in acetone (25 ml) and water (5 ml) was treated with concentrated hydrochloric acid (0.2 ml) and the mixture heated to reflux for 4 hours. The cooled mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic extract was dried and evaporated to give a white solid (0.4g). Chromatography gave the title compound (0.2g, 46%).

20 25 MS (+ve ion electrospray) m/z 301 (MH⁺).

(g) Title compound

A solution of Example (8f) (0.17g, 0.6 mmol) in methanol (5ml) was treated with heptylamine (0.13ml, 0.1g, 0.85 mmol) and sodium triacetoxyborohydride (0.18g, 0.85 mmol). After 3 hours the mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic extract was dried and evaporated to give a white solid (0.3g). Chromatography gave the title compound (0.13g, 60%).

MS (+ve ion electrospray) m/z 400 (MH⁺).

30

Example 9. 4-(N-Ethoxycarbonylmethyl-N-heptylamino)-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine oxalate

4-Heptylamo-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine (Example 6) (100mg) was alkylated with ethyl bromoacetate (0.026ml) in the presence of potassium carbonate (105mg) in dimethylformamide (3ml). After removal of solvent, the crude product was dissolved in dichloromethane and washed with water. Chromatography

on silica gel (10% methanol/ dichloromethane) gave the title compound (85mg, 70%). This was converted to the oxalate salt in the normal manner.
MS (+ve ion electrospray) m/z 486 (MH+).

5 **Example 10. 4-(N-Carboxymethyl-N-heptylamino)-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine oxalate**

The ester Example (9) (60mg) was hydrolysed in 2M hydrochloric acid at 100 °C. After evaporation to dryness, the product was triturated with ether. The salt obtained was converted to the free base, and then to the oxalate salt in the normal manner.

10 MS (+ve ion electrospray) m/z 458 (MH+).

Example 11. 4-(N-heptyl -N-2-hydroxyethylamino)-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate

15 The ester Example (9) (60mg) was dissolved in dry tetrahydrofuran (2ml) and treated with lithium aluminium hydride (1M in ether, 0.14ml) at 0 °C for 3 hours. The mixture was treated with sodium hydroxide, and magnesium sulfate, filtered and evaporated to give the free base (38mg, 68%). This was converted to the dioxalate salt in the normal manner.

MS (+ve ion electrospray) m/z 444 (MH+).

20

Example 12. 4-(N-Aminocarbonylmethyl-N-heptylamino)-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine oxalate

25 4-Heptylamino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine (Example 6) (100mg) was alkylated with 2-bromoacetamide (38mg) in the presence of potassium carbonate (105mg) in dimethylformamide (5ml). After removal of solvent, the crude product was dissolved in dichloromethane and washed with water. Chromatography on silica gel (dichloromethane) gave the title compound (43mg, 38%). This was converted to the dioxalate salt in the normal manner.

MS (+ve ion electrospray) m/z 457 (MH+).

30

Example 13. 4-(N-2-Aminoethyl-N-heptylamino)-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine tetrahydrochloride

35 4-Heptylamino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine (Example 6) (190mg) was acylated with a mixture of N-tert-butoxycarbonylglycine (87mg), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (230mg) and N-methyl morpholine (0.11ml) in dry dichloromethane (10ml). The mixture was poured into water and extracted with dichloromethane. The extract was washed with water and brine,

dried and evaporated. The crude product was chromatographed on silica gel (2-10% methanol/dichloromethane) to give a mixture of N- acylated and N,O-diacylated products (86mg).

The above acylated mixture (43mg) was reduced with lithium aluminium hydride as in Example (11). Chromatography on silica gel (dichloromethane) gave an N-(2-tert-butoxycarbonylaminoethyl) product (15 mg) which was heated in 5M hydrochloric acid at 100 °C. Evaporation to dryness gave the title compound (12mg).
MS (+ve ion electrospray) m/z 443 (MH+).

10 **Example 14. 4-(N-3-Ethoxycarbonylallyl-N-heptylamino)-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine**

4-Heptylamino-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine (Example 6) (200mg) was alkylated with ethyl 4-bromocrotonate (96mg) in the presence of potassium carbonate (210mg) in dimethylformamide (10ml). After removal of solvent, the crude product was dissolved in dichloromethane and washed with water. Chromatography on silica gel (dichloromethane) gave the title compound (43mg, 17%).
MS (+ve ion electrospray) m/z 512 (MH+).

20 **Example 15. 4-(N-3-Carboxyallyl-N-heptylamino)-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine trihydrochloride**

The ester Example (14) (35mg) was hydrolysed in 5M hydrochloric acid at 100 °C. Evaporation to dryness gave the title compound (60mg).
MS (+ve ion electrospray) m/z 484 (MH+).

25 **Example 16. 4-Heptylamino-4-methoxycarbonyl-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate**

(a) Methyl 4-amino-1-tert-butoxycarbonylpiperidine-4-carboxylate

4-Amino-1-tert-butoxycarbonylpiperidine-4-carboxylate (5g) in acetonitrile (22ml) and methanol (2ml) was treated with di-isopropylethylamine (3.65ml) and trimethylsilyldiazomethane (2M in hexane, 13.9ml). After overnight stirring and evaporation of solvent, the crude product was chromatographed on silica gel (0-50% ethyl acetate/petrol) to give a yellow oil (4g, 76%).

MS (+ve ion electrospray) m/z 259 (MH+).

(b) Methyl 1-tert-butoxycarbonyl-4-heptylamino piperidine-4-carboxylate

A solution of the aminoester (16a) (3.77g) in methanol (40ml) was treated with heptaldehyde (2.03ml) and stirred for 2 hours. Sodium triacetoxyborohydride (3.43g) was added and the mixture was stirred for 16hours. Solvent was evaporated and the residue

was dissolved in dichloromethane, washed with water, dried and evaporated, to give a yellow oil (4.34g, 83%).

MS (+ve ion electrospray) m/z 357 (MH⁺).

(c) Methyl 4-heptylaminopiperidine-4-carboxylate

5 To a solution of the tert-butoxycarbonylpiperidine (16b) (0.2g) in dichloromethane (1ml) was added trifluoroacetic acid (1ml). When hydrolysis was complete the mixture was extracted with water. The aqueous extract was washed with ether, basified with sodium hydrogen carbonate and saturated with sodium chloride, then extracted with 5% methanol/dichloromethane. The extract was dried and evaporated to give a yellow oil (90

10 mg, 63%).

MS (+ve ion electrospray) m/z 257 (MH⁺).

(d) Title compound

A mixture of the piperidine (16c) (0.5g), oxirane Example 1(a) (0.43g) and lithium perchlorate (0.28g) in acetonitrile (2ml) was stirred for 3 days at room 15 temperature, then heated at 50 °C for 16 hours. Solvent was evaporated and the residue was dissolved in dichloromethane, washed with water, dried and evaporated. The crude product was chromatographed on silica gel (ethyl acetate) to give the free base (0.35g, 39%), which was converted to the dioxalate salt in the normal manner.

MS (+ve ion electrospray) m/z 458 (MH⁺).

20

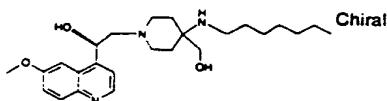
Example 17. 4-Carboxy-4-Heptylamo-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine trihydrochloride

The ester Example (16) (50mg) was heated under reflux in 2M hydrochloric acid for 18 hours. Evaporation to dryness and trituration with ethyl acetate and ether gave the 25 title compound (51mg).

MS (+ve ion electrospray) m/z 444 (MH⁺).

Example 18. 4-Heptylamo-4-hydroxymethyl-1-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)]ethylpiperidine dioxalate

30



The ester Example (16) (60mg) was reduced with lithium aluminium hydride as in Example (11). Chromatography on silica gel (0-20% methanol/dichloromethane) gave the 35 title compound (31mg).

MS (+ve ion electrospray) m/z 430 (MH⁺).

¹H NMR (CDCl₃): δ 0.88 (3H, t, J=7), 1.28 (8H, m), 1.46 (2H, m), 1.68 (4H, m), 2.41-2.58 (5H, m), 2.73 (1H, quintet, J=5), 2.85 (2H, dd, J=12,3), 3.38 (2H,s), 3.93 (3H,s), 5.43 (1H, dd, J=13,3), 7.18 (1H,d, J=3), 7.37 (1H, dd,J=9,3), 7.63 (1H, d, J=4.5), 8.03 (1H, d, J=9), 8.77 (1H, d ,J=4.5)

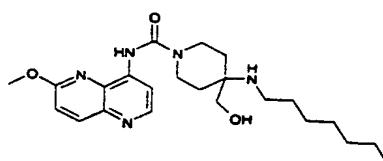
5 The free base was converted to the dioxalate salt in the normal manner, giving a white solid.

Example 19. 4-Heptylamino-4-methoxycarbonyl-1-(6-methoxy-[1,5]-naphthyridine-4-yl)aminocarbonylpiperidine

10 A solution of amine (8d) (0.26g) in chloroform (7ml) was treated with 4-dimethylaminopyridine (0.2g) and 1,1'-carbonyldiimidazole (0.44g) and stirred for 18 hours. The solvent was evaporated and replaced with dimethyl formamide (5ml). The piperidine ester Example (16c) (0.46g) was added and the mixture was stirred for 2 hours at 100 °C. The mixture was diluted with water and extracted with ethyl acetate. The 15 extract was washed with brine, dried and evaporated. The crude product was chromatographed on silica gel (1:1 hexane/ethyl acetate) to give the free base (0.25g, 34%).

MS (+ve ion electrospray) m/z 458 (MH⁺).

20 **Example 20. 4-Heptylamino-4-hydroxymethyl-1-(6-methoxy-[1,5]-naphthyridine-4-yl)aminocarbonylpiperidine**



25 The ester Example (19) (0.1g) was reduced with lithium aluminium hydride as in Example 11. The reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water and brine, dried and evaporated. The crude product was chromatographed on silica gel (0-1% methanol/ dichloromethane) to give the title compound (50mg, 53%) as a white solid.

30 MS (+ve ion electrospray) m/z 430 (MH⁺).

¹H-NMR (CDCl₃): δ 0.88(3H,t,J=7Hz), 1.28(8H,m), 1.47(2H,m), 1.70(4H,m), 2.51(2H,t,J=7Hz), 3.452H,s), 3.59(2H,dm,J=13Hz), 3.73(2H,dm,J=13Hz), 4.05(3H,s), 7.13(1H,d,J=9Hz), 8.20(1H,d,J=9Hz), 8.31(1H,d,J=5Hz), 8.64(1H,d,J=5Hz), 9.08(1H,s).

Biological Activity

The MIC ($\mu\text{g/ml}$) of test compounds against various organisms was determined:
S. aureus Oxford, S. aureus WCUH29, S. pneumoniae 1629, S. pneumoniae N1387,
S. pneumoniae ERY 2.

5 Example 4 has an MIC of less than or equal to $1\mu\text{g/ml}$ against one or more of the above range of gram positive and gram negative bacteria.